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## Endoscopic ultrasound-guided treatments: Are we getting evidence based - a systematic review

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### Abstract

The continued need to develop less invasive alternatives to surgical and radiologic interventions has driven the development of endoscopic ultrasound (EUS)-guided treatments. These include EUS-guided drainage of pancreatic fluid collections, EUS-guided necrosectomy, EUS-guided cholangiography and biliary drainage, EUS-guided pancreatography and pancreatic duct drainage, EUS-guided gallbladder drainage, EUS-guided drainage of abdominal and pelvic fluid collections, EUS-guided celiac plexus block and celiac plexus neurolysis, EUS-guided pancreatic cyst ablation, EUS-guided vascular interventions, EUS-guided delivery of antitumoral agents and EUS-guided fiducial placement and brachytherapy. However these procedures are technically challenging and require expertise in both EUS and in-

terventional endoscopy, such as endoscopic retrograde cholangiopancreatography and gastrointestinal stenting. We undertook a systematic review to record the entire body of literature accumulated over the past 2 decades on EUS-guided interventions with the objective of performing a critical appraisal of published articles, based on the classification of studies according to levels of evidence, in order to assess the scientific progress made in this field.

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**Key words:** Endoscopic ultrasound; Pseudocyst drainage; Necrosectomy; Celiac plexus neurolysis; Levels of evidence; Fine needle injection

**Core tip:** Endoscopic ultrasound (EUS)-guided interventions have become increasingly popular. The advantages of EUS guidance over percutaneous and surgical routes are well established for pseudocyst drainage and celiac plexus neurolysis as they have been assessed in high level of evidence literature. However, for other very fashionable procedures such as bile duct and pancreatic duct drainage, the role of EUS guidance has only been reported as preliminary studies in limited number of patients. The level of evidence of each EUS-guided intervention is accurately reported in this review in order to provide the readers with the current status of knowledge and allow insights into potential future direction of research.

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## INTRODUCTION

Endoscopic ultrasound (EUS) has evolved from a purely diagnostic imaging modality to an interventional procedure that provides a minimally invasive alternative to interventional radiologic and surgical techniques.

Several innovative techniques now constitute the portfolio of interventional EUS, such as EUS-guided drainage (GD) of pancreatic fluid collections (PFCs), EUS-guided necrosectomy, EUS-guided cholangiography and biliary drainage (BD), EUS-guided pancreatography and pancreatic duct drainage (PDD), EUS-guided gallbladder drainage, EUS-GD of abdominal and pelvic fluid collections, EUS-guided celiac plexus block (CPB) and celiac plexus neurolysis (CPN), EUS-guided pancreatic cyst ablation, EUS-guided delivery of antitumoral agents and EUS-guided fiducial placement, brachytherapy and EUS-guided vascular interventions. However, EUS-guided treatments are technically challenging and require expertise in both standard diagnostic EUS and endoscopic interventional procedures, such as endoscopic retrograde cholangiopancreatography (ERCP) and gastrointestinal stenting.

For such a reason, it is important that we carefully monitor the results of our EUS-guided treatments in order to either implement them in clinical practice or abandon/thoroughly revise them. Evidence based medicine is known as a strategic tool to do so.

Following our previous systematic analysis of the levels of evidence (LE) of the EUS literature<sup>[1-4]</sup>, we reviewed the entire body of literature accumulated over the past 2 decades on EUS-guided treatments. Our main aim was to critically appraise the published articles, based on the classification of studies according to LE, in order to assess the scientific progress made in this field.

All articles relevant to EUS-guided interventional procedures were extracted up to September 2013. Moreover, the references of reviewed articles were scrutinized to obtain any other reference that eluded the primary search.

This review is based on the results of searches carried out in PubMed and Google Scholar. Original research articles [randomized controlled trials (RCT), prospective studies (PS) and retrospective studies (RS)], meta-analyses, systematic reviews and surveys pertinent to EUS-guided interventional procedures were included.

Studies enrolling up to 10 patients were categorized as case series. We also included letters and case reports describing recent, innovative or original EUS-guided treatments. Commentaries, non-English language articles, congress proceedings and abstracts, and articles in which EUS did not represent the principal matter were not included.

In regard to data collection, priority was assigned to the study subject, design and methods, the type and year of publication and the number of patients enrolled. The content of each study was further analyzed to identify relevant clinical issues. In particular, when the same

group of patients from the same institution was included in two consecutive papers (*e.g.*, preliminary study and final results study), we included only the data from the most recent one to avoid duplicated results.

Levels of evidence were stratified according to the North of England evidence-based guidelines<sup>[5,6]</sup>. LE I a: Evidence obtained from meta-analysis of RCTs; LE I b: Evidence obtained from at least one RCT; LE II a: Evidence obtained from at least one well designed controlled study without randomization; LE II b: Evidence obtained from at least one other type of well-designed quasi-experimental study; LE III: Evidence obtained from well-designed non-experimental descriptive studies such as comparative studies, correlation studies, and case studies; LE IV: Evidence obtained from expert committee reports or opinions, or clinical experiences of respected authorities.

A total of 381 pertinent articles were finally included for the purpose of this systematic review. Published research focused primarily on EUS-guided cholangiography and biliary drainage (85 studies), followed by EUS-GD of pancreatic fluid collections (84 studies), EUS-guided CPN or CPB (52 studies), EUS-guided tumor ablation (34 studies), EUS-guided ethanol ablation (28 studies), EUS-guided fiducial placement (26 studies), EUS-guided vascular interventions (23 studies), EUS-guided necrosectomy (20 studies), EUS-guided pancreatography and pancreatic duct drainage (15 studies), EUS-guided gallbladder drainage (7 studies) and EUS-GD of abdominal (non-peripancreatic) and pelvic collections (7 studies). A detailed classification of the studies according to the subclasses and the corresponding LE is presented in Table 1. As expected, we identified a predominance of LE III and IV articles in all types of EUS-guided treatments, reflecting the relative novelty of these techniques. Nevertheless, a fair number of high LE articles (LE I a and I b) were identified for EUS-GD of pancreatic fluid collections and EUS-guided CPN, forming a solid base of evidence for these established indications. On the other hand, novel therapeutic applications, such as EUS-guided cholangiography and biliary drainage and EUS-guided tumor ablation, still lack relevant clinical data and should still be considered strictly investigational. A focused description of all forms of EUS-guided treatment is given below, in a schematic format.

## EUS-GUIDED DRAINAGE OF PFCs

EUS-GD is regarded as an established technique for the treatment of PFCs. Up to now, the reported evidence pertains about 2115 patients enrolled in safety and efficacy studies overall<sup>[7-64]</sup>. Mean technical and clinical success rates reported in series with more than 10 patients were 97% and 90%, respectively and mean overall recurrence rate was 8%<sup>[8-64]</sup> (Table 2). The mean overall complication rate was 17% including bleeding (69 cases), superinfection (52 cases), stents migration that required endoscopic reintervention (51 cases), perforation treated with surgery

**Table 1** Level of evidence per subject

Level of evidence	I a	I b	II a	II b	III	IV	Total
EUS-GD of pancreatic fluid collections	1	5	0	16	42	20	84
EUS-guided necrosectomy	1	1	0	0	15	3	20
EUS-guided cholangiography and biliary drainage	0	1	0	7	37	40	85
EUS-guided pancreatography and pancreatic duct drainage	0	0	0	0	9	6	15
EUS-guided gallbladder drainage	0	1	0	3	1	2	7
EUS-GD of abdominal (non-peripancreatic) and pelvic collections	0	0	0	2	3	2	7
EUS-guided Celiac Plexus Neurolysis or Block	4	7	1	5	16	19	52
EUS-guided ethanol ablation	0	1	0	5	13	9	28
EUS-guided tumor ablation	0	0	0	9	4	21	34
EUS-guided fiducial placement	0	0	0	2	10	14	26
EUS-guided vascular intervention	0	1	0	2	15	5	23
Total	6	17	1	51	165	141	381

EUS-GD: Endoscopic ultrasound-guided drainage.

(27 cases) and pneumoperitoneum treated conservatively (18 cases). However, only 5 cases of death were deemed to be procedure related<sup>[8-64]</sup>.

**EUS vs surgical drainage**

A recent RCT<sup>[62]</sup> comparing EUS and surgery for pancreatic pseudocyst drainage, showed no pseudocyst recurrence during the follow-up in the former group and no evidence that surgical cystogastrostomy was superior to EUS. Moreover, EUS treatment was associated with shorter hospital stay, better physical and mental health of patients, and lower costs. EUS-GD of PFCs is not inferior to surgical drainage in terms of safety and efficacy (LE I b).

**EUS vs blind endoscopic drainage**

Meta-analysis of EUS-GD of PFCs showed superior technical and treatment success rates and more favorable safety profiles than traditional non-EUS guided drainage<sup>[65]</sup> (LE I a).

Varadarajulu *et al*<sup>[26]</sup> published the first RCT, randomizing 30 patients to undergo either EUS-GD or endoscopic conventional transmural drainage (ECTD). All patients assigned to EUS underwent successful drainage (100%), while the procedure was technically successful in only 5/15 patients (33%) assigned to ECTD. All 10 patients who failed drainage by ECTD underwent successful drainage of the PFC on a crossover to EUS. Major procedure-related bleeding was encountered in 2 patients in whom ECTD was performed (LE I b). Park *et al*<sup>[30]</sup> enrolled 60 patients in a RCT with the same design as above. Technical success of the drainage was significantly higher in the EUS group (94%) than in the ECTD group (72%) ( $P = 0.039$ ) in intention-to-treat analysis. In 8 cases where ECTD had failed because of non-bulging PFCs, crossover to EUS-GD was always successful. Complications occurred in 7% of the EUS group *vs* 10% of the ECTD group ( $P = NS$ ). During follow-up, PFC resolution was achieved in 97% in the EUS group and in 91% in the ECTD group ( $P = NS$ ) (LE I b). EUS-GD of PFCs has superior technical and clinical outcomes compared to blind endoscopic drainage (LE I a).

**Forward view vs linear scanning EUS**

EUS-GD of PFCs is commonly performed with linear scanning echoendoscopes, whose tangential approach to PFCs may be challenging for operators. Theoretically, technical difficulties might be overcome using a forward-viewing echoendoscope which allows a straight approach to PFCs. However, a recent RCT<sup>[45]</sup> comparing the performance of linear *vs* forward-viewing echoendoscopes in draining PFCs failed to demonstrate any significant difference in technical success, mean procedure time, safety or efficacy between the two types of echoendoscopes.

The use of forward-viewing echoendoscope for EUS-guided drainage of PFCs does not confer any significant advantage in terms of safety and efficacy compared to the use of linear scanning echoendoscope (LE I b).

**Timing of stent removal**

In order to evaluate the incidence of PFCs recurrence after successful EUS-GD, 28 patients were randomized either to stent removal ( $n = 13$ ) or to stent left in place ( $n = 15$ ) and were followed up for a median period of 14 months. PFCs recurrence was observed in 5 patients in the stent retrieval group, as opposed to none in the other group ( $P = 0.013$ )<sup>[20]</sup>. After successful EUS-GD of PFCs, stent retrieval is associated with higher recurrence rate than leaving stent in place (LE I b).

**Nasocystic drainage to maintain patency:** Siddiqui *et al*<sup>[60]</sup> evaluated in a RS EUS-guided nasocystic drainage alongside transmural stents in PFCs with viscous solid debris. Association with the nasocystic drainage resulted in lower stent occlusion rate and better short-term clinical outcomes compared to those patients who underwent standard EUS-GD. The placement of a nasocystic drainage may increase the clinical success rate, especially in PFCs containing abundant debris (LE III).

**Multiple transluminal gateway technique:** Varadarajulu *et al*<sup>[42]</sup>, showed that drainage of necrotic PFCs with multiple instead of a single transmural access, placing multiple stents and a nasocystic drainage in each tract, led to better long-term clinical outcomes. Multiple instead of

**Table 2** Endoscopic ultrasound-guided drainage of pancreatic fluid collections

Ref.	Design	Cases	Technical success	Clinical success	Recurrence	Complications <sup>1</sup>
Binmoeller <i>et al</i> <sup>[8]</sup>	RS	27	93%	78%	22%	52%
Pfaffenbach <i>et al</i> <sup>[9]</sup>	PS	11	91%	82%	18%	None
Giovannini <i>et al</i> <sup>[10]</sup>	PS	35	100%	89%	9%	3%
Norton <i>et al</i> <sup>[11]</sup>	RS	14	93%	93%	23%	14%
Vosoghi <i>et al</i> <sup>[12]</sup>	RS	14	100%	93%	7%	7%
Enya <i>et al</i> <sup>[13]</sup>	PS	13	100%	85%	0%	None
Hookey <i>et al</i> <sup>[14]</sup>	RS	32	96%	93%	12%	11%
Krüger <i>et al</i> <sup>[15]</sup>	PS	35	94%	88%	12%	33%
Azar <i>et al</i> <sup>[16]</sup>	RS	23	91%	82%	18%	4%
Antillon <i>et al</i> <sup>[17]</sup>	PS	33	94%	87%	4%	15%
Kahaleh <i>et al</i> <sup>[18]</sup>	PS	46	100%	93%	NR	19%
Ahlawat <i>et al</i> <sup>[19]</sup>	PS	11	100%	82%	18%	18%
Arvanitakis <i>et al</i> <sup>[20]</sup>	RCT	46	100%	94%	11%	22%
Lopes <i>et al</i> <sup>[21]</sup>	RS	51	94%	84%	17%	25%
Varadarajulu <i>et al</i> <sup>[22]</sup>	PS	23	100%	95%	0%	None
Lopes <i>et al</i> <sup>[23]</sup>	PS	31	100%	94%	19%	26%
Ardengh <i>et al</i> <sup>[24]</sup>	PS	77	94%	91%	11%	6%
Varadarajulu <i>et al</i> <sup>[25]</sup>	RS	20	100%	95%	NR	None
Varadarajulu <i>et al</i> <sup>[26]</sup>	RCT	24	100%	96%	NR	4%
Varadarajulu <i>et al</i> <sup>[27]</sup>	PS	60	95%	93%	4%	2%
Barthet <i>et al</i> <sup>[28]</sup>	PS	28	100%	89%	NR	25%
Talreja <i>et al</i> <sup>[29]</sup>	PS	18	100%	95%	0%	44%
Park <i>et al</i> <sup>[30]</sup>	RCT	39	95%	95%	6%	7%
Yasuda <i>et al</i> <sup>[31]</sup>	RS	26	92%	87%	17%	None
Itoi <i>et al</i> <sup>[32]</sup>	PS	13	100%	100%	0%	None
Varadarajulu <i>et al</i> <sup>[33]</sup>	PS	10	100%	90%	0%	None
Ang <i>et al</i> <sup>[34]</sup>	PS	10	100%	100%	0%	10%
Ahn <i>et al</i> <sup>[35]</sup>	RS	47	98%	100%	11%	11%
Jazrawi <i>et al</i> <sup>[36]</sup>	RS	10	100%	100%	10%	None
Sadik <i>et al</i> <sup>[37]</sup>	PS	26	100%	88%	4%	15%
Will <i>et al</i> <sup>[38]</sup>	PS	132	97%	96%	15%	29%
Seicean <i>et al</i> <sup>[39]</sup>	PS	24	83%	79%	0%	17%
Heinzow <i>et al</i> <sup>[40]</sup>	RS	42	88%	78%	21%	21%
Varadarajulu <i>et al</i> <sup>[41]</sup>	PS	148	100%	99%	NR	5%
Varadarajulu <i>et al</i> <sup>[42]</sup>	RS	60 <sup>2</sup>	100%	69%	0%	8%
Varadarajulu <i>et al</i> <sup>[43]</sup>	RS	20	100%	100%	5%	None
Zheng <i>et al</i> <sup>[44]</sup>	PS	14	90%	90%	0%	19%
Voermans <i>et al</i> <sup>[45]</sup>	RCT	52	100%	82%	9%	11%
Mangiavillano <i>et al</i> <sup>[46]</sup>	PS	21	86%	81%	14%	5%
Seewald <i>et al</i> <sup>[47]</sup>	RS	80	97%	83%	13%	26%
Itoi <i>et al</i> <sup>[48]</sup>	RS	15	100%	100%	0%	6%
Puri <i>et al</i> <sup>[49]</sup>	PS	40	100%	97%	2%	7%
Fabbri <i>et al</i> <sup>[50]</sup>	PS	20	100%	95%	5%	15%
Rasmussen <i>et al</i> <sup>[51]</sup>	RS	22	86%	86%	18%	18%
Khashab <i>et al</i> <sup>[52]</sup>	RS	10	100%	100%	0%	None
Penn <i>et al</i> <sup>[53]</sup>	PS	20	100%	85%	18%	15%
Weilert <i>et al</i> <sup>[54]</sup>	PS	18	100%	78%	NR	33%
Rana <i>et al</i> <sup>[55]</sup>	RS	20 <sup>2</sup>	100%	100%	0%	5%
Binmoeller <i>et al</i> <sup>[56]</sup>	RS	14	100%	79%	NR	21%
Nan <i>et al</i> <sup>[57]</sup>	RS	21	100%	100%	NR	5%
Kato <i>et al</i> <sup>[58]</sup>	RS	67	88%	83%	15%	1%
Künzli <i>et al</i> <sup>[59]</sup>	RS	108	97%	84%	18%	20%
Siddiqui <i>et al</i> <sup>[60]</sup>	RS	88	99%	79%	3%	30%
Rische <i>et al</i> <sup>[61]</sup>	RS	18	100%	94%	6%	33%
Varadarajulu <i>et al</i> <sup>[62]</sup>	RCT	20	100%	95%	0%	None
Total	55 studies	1867	97% (83%-100%)	90% (69%-100%)	8% (0%-23%)	17% (0%-52%)

<sup>1</sup>Complications include: early and late, procedural and stent related; <sup>2</sup>Only patients with walled-off pancreatic necrosis. RCT: Randomized controlled trial; PS: Prospective study; RS: Retrospective study; NR: Not reported.

single transmural points of access allow better drainage of the necrotic contents and improve treatment success (LE III).

**Use of covered self-expandable metal stents:** Covered

self-expandable metal stents have been recently tested for drainage of PFCs and walled-off pancreatic necrosis with the intent of creating a larger fistula compared to plastic stents. Increased success rate and reduced time to resolution were shown in case series and pilot studies<sup>[48,50,53,54]</sup>

**Table 3** Endoscopic ultrasound-guided necrosectomy

Ref.	Design	Cases	Technical success	Clinical success	Recurrence	Complications <sup>1</sup>
Seewald <i>et al</i> <sup>[70]</sup>	RS	13	100%	85%	15%	30%
Charnley <i>et al</i> <sup>[71]</sup>	RS	13	100%	92%	0%	None
Voermans <i>et al</i> <sup>[72]</sup>	RS	25	100%	93%	7%	40%
Hocke <i>et al</i> <sup>[73]</sup>	RS	30	97%	83%	3%	23%
Schrover <i>et al</i> <sup>[74]</sup>	RS	8	100%	75%	12%	25%
Mathew <i>et al</i> <sup>[75]</sup>	RS	6	100%	100%	0%	None
Escourrou <i>et al</i> <sup>[76]</sup>	RS	13	100%	100%	0%	46%
Jürgensen <i>et al</i> <sup>[77]</sup>	RS	35	100%	97%	0%	17%
Bakker <i>et al</i> <sup>[78]</sup>	RCT	10	100%	100%	20%	40%
Will <i>et al</i> <sup>[79]</sup>	RS	18	100%	100%	11%	17%
Rische <i>et al</i> <sup>[61]</sup>	RS	22	100%	86%	14%	36%
Yamamoto <i>et al</i> <sup>[80]</sup>	RS	4	100%	50%	NR	25%
Hritz <i>et al</i> <sup>[81]</sup>	RS	4	100%	100%	0%	None
Yasuda <i>et al</i> <sup>[82]</sup>	RS	57	100%	75%	7%	33%
Ang <i>et al</i> <sup>[83]</sup>	RS	8	100%	87%	13%	None
Sarkaria <i>et al</i> <sup>[84]</sup>	RS	17	100%	88%	0%	6%
Total	16 studies	283	100% (97%-100%)	88% (50%-100%)	7% (0%-20%)	28% (0%-46%)

<sup>1</sup>Complications include: early and late, procedural and stent related. RCT: Randomized controlled trial; PS: Prospective study; RS: Retrospective study; NR: Not reported.

(LE II b). However stents designed for other indications were used. Recently, new devices have been introduced for the purpose of PFCs drainage, provided with larger diameter and antimigration features such as the “NAGI” stent (Taewoong-Medical Co, Seoul, South Korea) or the “AXIOS” stent (Xlumena Inc., Mountain View, California, United States)<sup>[66,67]</sup>.

A case series<sup>[68]</sup> described the use of the AXIOS stent in 9 patients who underwent EUS-guided drainage of PFCs. The technical success rate was 89% (8/9) due to one failure of the delivery system and all patients had successful outcome achieving complete PFC resolution. One patient developed a tension pneumothorax immediately after transesophageal drainage. No migrations were reported, and all stents were removed easily. Only one patient presented a recurrence 4 wk after stent removal. Use of covered self-expandable metal stents seems to improve the clinical outcome in these patients; however, larger studies comparing metal and plastic stents are warranted (LE II b).

## EUS-GUIDED NECROSECTOMY

Debridement of pancreatic necrosis has traditionally been managed surgically. In recent years, EUS-guided endoscopic necrosectomy has become an alternative.

This technique involves a transmural (transgastric or transduodenal) EUS-guided access to the necrotic area, followed by large caliber (*e.g.*, 18 mm) balloon dilation of the tract between the collection and the gastrointestinal wall, allowing for passage of a gastroscop into the collection to visualize the necrotic material. A variety of tools, such as baskets, snares, and nets have been used to remove the necrotic tissue. EUS-guided necrosectomy has been reported in 283 published cases so far. In the published studies a median of 4 (1-35) sessions was required to achieve resolution of the necrotic collection<sup>[69]</sup>.

Mean technical and clinical success rates reported were 100% and 88%, respectively; mean overall complication rate was 28% and mean overall recurrence rate was 7%<sup>[61,70-84]</sup> (Table 3). A recent RCT<sup>[78]</sup> by the Dutch Pancreatitis Study Group showed a lower rate of proinflammatory response, organ failure and major complications in patients undergoing EUS-guided necrosectomy as compared to surgical necrosectomy (LE I b).

## EUS-GUIDED CHOLANGIOGRAPHY AND BILIARY DRAINAGE

When biliary ductal access *via* endoscopic retrograde cholangiopancreatography (ERCP) fails, rescue measures include precut papillotomy, percutaneous transhepatic biliary drainage (PTBD), surgical bypass and EUS-guided BD. Three different EUS-guided BD approaches have been described: direct transluminal stenting *via* transgastric or transduodenal route, rendezvous technique passing a guidewire through an intrahepatic or extrahepatic access to the papilla, and antegrade stent placement.

EUS-guided BD has currently been performed in 1127 published cases, with mean technical and clinical success rates of 91% and 88%, respectively. However, mean overall complication rate was 26% with mortality of 0.4% (4/1127 patients)<sup>[85-113]</sup> (Table 4).

### EUS-guided BD vs percutaneous BD

In a recent RCT 25 patients with unresectable malignant biliary obstruction and a previous failed ERCP attempt were assigned either to EUS-guided or to percutaneous transhepatic BD. The authors reported 100% technical and clinical success in both study groups, with no difference in incidence of adverse events<sup>[99]</sup> (LE I b). Combining EUS and ERCP in the same procedure was a cost saving strategy compared to referring the patient for

**Table 4** Endoscopic ultrasound-guided cholangiography and biliary drainage

Ref.	Design	Cases	Technical success	Clinical success	Complications <sup>1</sup>
Bories <i>et al</i> <sup>[86]</sup>	RS	11	91%	80%	72%
Maranki <i>et al</i> <sup>[87]</sup>	RS	49	84%	80%	18%
Brauer <i>et al</i> <sup>[88]</sup>	PS	12	92%	72%	16%
Horaguchi <i>et al</i> <sup>[89]</sup>	PS	16	100%	94%	37%
Kim <i>et al</i> <sup>[90]</sup>	RS	15	80%	80%	None
Fabbri <i>et al</i> <sup>[91]</sup>	PS	16	75%	75%	8%
Park <i>et al</i> <sup>[92]</sup>	RS	57	96%	89%	47%
Hara <i>et al</i> <sup>[93]</sup>	PS	18	94%	94%	77%
Komaki <i>et al</i> <sup>[94]</sup>	RS	15	100%	100%	46%
Ramírez-Luna <i>et al</i> <sup>[95]</sup>	PS	11	91%	82%	18%
Shah <i>et al</i> <sup>[96]</sup>	RS	68	85%	85%	9%
Iwashita <i>et al</i> <sup>[97]</sup>	RS	40	73%	73%	12% <sup>2</sup>
Dhir <i>et al</i> <sup>[98]</sup>	RS	58	98%	98%	3%
Artifon <i>et al</i> <sup>[99]</sup>	RCT	13	100%	100%	15%
Song <i>et al</i> <sup>[100]</sup>	PS	15	87%	87%	47%
Kim <i>et al</i> <sup>[101]</sup>	PS	13	92%	84%	38%
Vila <i>et al</i> <sup>[102]</sup>	RS	106	70%	70%	23%
Horaguchi <i>et al</i> <sup>[103]</sup>	RS	21	100%	100%	10%
Hara <i>et al</i> <sup>[104]</sup>	PS	18	94%	89%	27%
Park <i>et al</i> <sup>[105]</sup>	PS	45	91%	87%	11%
Kawakubo <i>et al</i> <sup>[106]</sup>	RS	14	100%	100%	14%
Dhir <i>et al</i> <sup>[107]</sup>	RS	35	97%	97%	23%
Khashab <i>et al</i> <sup>[108]</sup>	RS	35	94%	91%	14%
Gornals <i>et al</i> <sup>[109]</sup>	RS	15	87%	73%	40%
Gupta <i>et al</i> <sup>[110]</sup>	RS	240	99%	87%	35%
Dhir <i>et al</i> <sup>[111]</sup>	RS	68	97%	97%	21% <sup>3</sup>
Kawakubo <i>et al</i> <sup>[112]</sup>	RS	64	95%	95%	42%
Total	27 studies	1088	91% (70%-100%)	87% (70%-100%)	29% (3%-77%)

<sup>1</sup>Complications include: early and late, procedural- and stent-related; <sup>2</sup>2.5% mortality (1 patient); <sup>3</sup>4% mortality (3 patients). RCT: Randomized controlled trial; PS: Prospective study; RS: Retrospective study; NR: Not reported.

percutaneous transhepatic BD<sup>[109]</sup> (LE III). EUS-guided BD appears to be a valid alternative to percutaneous BD, showing similar efficacy and safety (LE I b). However, data are still very preliminary and large RCT are needed to demonstrate whether EUS can represent a valid alternative to percutaneous route in this setting.

#### **EUS-guided rendezvous BD vs precut papillotomy**

The outcome of 58 patients undergoing EUS-guided rendezvous drainage because of bile duct obstruction, after failed selective biliary cannulation, was compared to an historical cohort of 144 patients treated with precut papillotomy. Treatment success was significantly higher for the EUS-guided rendezvous patients than for those who underwent precut papillotomy, while there was no difference in complications rate<sup>[98]</sup>. EUS-guided rendezvous drainage seems to be superior to precut papillotomy in patients with bile duct obstruction after failed ERCP (LE III).

#### **EUS-guided rendezvous BD vs EUS-guided transluminal BD**

A recent RS (33 patients) compared the outcome of two different techniques in patients who underwent a standardized approach to EUS-guided BD, with an initial attempt at using the rendezvous technique ( $n = 13$ ) followed by the transluminal approach ( $n = 20$ ) in case of rendezvous failure. The Authors reported that both

techniques achieved the same effectiveness and safety<sup>[108]</sup>. Transluminal EUS-guided BD may represent a safe and effective alternative in case of failure of rendezvous technique (LE III).

#### **EUS-guided transhepatic BD vs EUS-guided extrahepatic BD**

EUS-guided BD can be performed either *via* intrahepatic (through the stomach) or *via* extrahepatic (through the duodenum) route. In a recent RS, despite similar technical and clinical success rate, extrahepatic access was associated with significantly shorter procedure and hospitalization time and with less complications<sup>[107]</sup> (LE III). Another multicenter RS enrolling 68 patients who underwent transluminal EUS-guided BD for malignant obstructive jaundice showed similar technical and clinical success both in patients who underwent transhepatic and extrahepatic drainage. However, transhepatic access was burdened with a significantly higher complication rate compared to the extrahepatic route (30.5% *vs* 9.3%,  $P = 0.03$ ); multivariate analysis identified the transhepatic route as the only factor independently related to the risk of procedure-related adverse event<sup>[111]</sup> (LE III). EUS-guided BD shows similar technical and clinical success rate with both transhepatic and extrahepatic access. However, extrahepatic access seems to be safer than transhepatic access (LE III).

**Table 5 Endoscopic ultrasound-guided pancreatography and pancreatic duct drainage**

Ref.	Design	Cases	Technical success	Clinical success	Complications <sup>1</sup>
Will <i>et al</i> <sup>[114]</sup>	RS	12	100% (SPDD: 67%)	50%	43%
Tessier <i>et al</i> <sup>[115]</sup>	RS	36	92% (SPDD: 92%)	69%	55%
Kahaleh <i>et al</i> <sup>[116]</sup>	RS	13	100% (SPDD: 77%)	77%	15%
Barkay <i>et al</i> <sup>[117]</sup>	RS	21	86% (SPDD: 48%)	86%	10%
Ergun <i>et al</i> <sup>[118]</sup>	RS	20	100% (SPDD: 90%)	72%	20%
Shah <i>et al</i> <sup>[96]</sup>	RS	25	100% (SPDD: 86%)	100%	16%
Vila <i>et al</i> <sup>[102]</sup>	RS	19	58% (SPDD: NR)	NR	26%
Kurihara <i>et al</i> <sup>[119]</sup>	RS	14	100% (SPDD: 93%)	93%	7%
Fujii <i>et al</i> <sup>[120]</sup>	RS	45	98% (SPDD: 73%)	53%	24%
Total	9 studies	205	100% (58%-100%)	74.5% (53%-100%)	20%(7%-55%)

<sup>1</sup>Complications include: early and late, procedural and stent related. SPDD: Successful pancreatic duct drainage; RS: Retrospective study; NR: Not reported.

## EUS-GUIDED PANCREATOGRAPHY AND PANCREATIC DUCT DRAINAGE

EUS-guided PDD has been reported in 248 published cases so far. They are usually indicated after failed ERCP in patients with benign conditions such as ductal stones, strictures or post-surgical stenosis<sup>[85,96,102,113-120]</sup> (Table 5).

### Outcomes of EUS-guided PDD

EUS-guided PDD is a challenging procedure and it is technically more demanding than EUS-guided BD. As a result, technical and clinical outcomes of EUS-guided PDD were less favorable than for EUS-guided BD with an overall technical success rate of 78%<sup>[96,102,113-120]</sup> (LE III). Technical failures were mainly due to difficult orientation of the echoendoscope along the axis of the pancreatic duct, inability to dilate the transmural tract because of dense fibrosis, and impossible endotherapy because of too acute angle of access to the pancreatic duct<sup>[96,102,113-120]</sup>. As a note of interest, successful ERCP was reported in some cases after EUS-guided pancreatography by needle injection of contrast medium with or without methylene-blue<sup>[96,117]</sup> (LE III). EUS-guided PDD is a challenging procedure, showing suboptimal clinical success and relevant complication rate (LE III).

### Technical issues and complications

EUS-guided rendezvous technique was usually attempted first, followed by the transenteric EUS-guided PDD in case of rendezvous failure<sup>[119]</sup> (LE III). EUS-guided transenteric stenting required more dilation of the needle tract than rendezvous technique, leading to serious adverse events such as pancreatitis (4%), pancreatic juice leakage (3%), bleeding (3%), and perforation (3%)<sup>[119]</sup> (LE III). The most common site for pancreatic duct access was through the gastric body, in view of the straight and stable echoendoscope position and the ease of access to the pancreatic duct<sup>[96,102,113-120]</sup> (LE III). Plastic stents were used for EUS-guided PDD unlike metal stents. In fact, covered metal stents can block side branches leading to obstructive pancreatitis and uncovered metal stents can cause pancreatic juice leakage between the stomach and pancreas<sup>[96,102,113-120]</sup> (LE III). EUS-guided PDD *via* tran-

senteric route shows higher complication rate than *via* rendezvous route (LE III).

## EUS-GUIDED GALLBLADDER DRAINAGE

Patients with acute cholecystitis unresponsive to medical therapy, require decompression of the gallbladder if they are unsuitable for emergency surgery. Available treatments are percutaneous transhepatic gallbladder drainage and EUS-guided gallbladder drainage. The latter has been performed in 97 published cases with mean technical and clinical success rates are 98% and 98%, respectively; overall mean complication rate was 16%<sup>[48,121-134]</sup> (Table 6).

### EUS-guided vs percutaneous gallbladder drainage

Recently a non-inferiority RCT<sup>[131]</sup> was conducted to evaluate the technical feasibility, efficacy and safety of EUS-guided *vs* percutaneous drainage in this setting. The authors enrolled 59 patients and reported similar technical success rate (97% *vs* 97%), clinical success (100% *vs* 96%) and rate of adverse events (7% *vs* 3%) in the two study groups (LE I b).

### Transgastric vs transduodenal approach

Both transgastric and transduodenal approaches have been performed to achieve EUS-guided gallbladder drainage. In a pilot study, plastic stent migration was observed in a patient 3 wk after trans-gastric drainage. The authors suggested that transduodenal approach toward the gallbladder neck could avoid plastic stent migration<sup>[127]</sup> (LE II b). On these basis, specific lumen-apposing metal stents with large distal and proximal flares have been developed<sup>[48,130,133]</sup>. EUS-guided gallbladder drainage shows similar feasibility, efficacy and safety profiles to percutaneous drainage (LE I b).

## EUS-GUIDED DRAINAGE OF ABDOMINAL NON-PERIPANCREATIC AND PELVIC COLLECTIONS

EUS-GD represents a valid treatment of fluid collections located in anatomic regions adjacent to the gastrointes-

**Table 6** Endoscopic ultrasound-guided drainage of gallbladder

Ref.	Design	Cases	Technical success	Clinical success	Complications <sup>1</sup>
Baron <i>et al</i> <sup>[121]</sup>	CR	1	100%	100%	None
Kwan <i>et al</i> <sup>[122]</sup>	RS	3	100%	100%	33%
Lee <i>et al</i> <sup>[123]</sup>	PS	9	100%	100%	11%
Takasawa <i>et al</i> <sup>[124]</sup>	CR	1	100%	100%	None
Kamata <i>et al</i> <sup>[125]</sup>	CR	1	100%	100%	None
Kamata <i>et al</i> <sup>[126]</sup>	CR	1	100%	100%	None
Song <i>et al</i> <sup>[127]</sup>	PS	8	100%	100%	37%
Súbtíl <i>et al</i> <sup>[128]</sup>	RS	4	100%	100%	25%
Itoi <i>et al</i> <sup>[129]</sup>	CR	2	100%	100%	None
Jang <i>et al</i> <sup>[130]</sup>	PS	15	100%	100%	13%
Jang <i>et al</i> <sup>[131]</sup>	RCT	30	97%	97%	7%
Itoi <i>et al</i> <sup>[48]</sup>	RS	5	100%	100%	None
Itoi <i>et al</i> <sup>[132]</sup>	CR	1	100%	100%	None
de la Serna-Higuera <i>et al</i> <sup>[133]</sup>	RS	13	85%	85%	15%
Widmer <i>et al</i> <sup>[134]</sup>	RS	3	100%	100%	None
Total	15 studies	97	100% (85%-100%)	100% (85%-100%)	0% (0%-37%)

<sup>1</sup>Complications include: early and late, procedural and stent related. RCT: Randomized controlled trial; PS: Prospective study; RS: Retrospective study; CR: Case report.

**Table 7** Endoscopic ultrasound-guided drainage of non-peripancreatic and pelvic collections

Ref.	Design	Cases	Technical success	Clinical success	Complications <sup>1</sup>
Attwell <i>et al</i> <sup>[135]</sup>	CR	1	100%	100%	None
Giovannini <i>et al</i> <sup>[136]</sup>	PS	12	100%	75%	25%
Seewald <i>et al</i> <sup>[137]</sup>	CR	2	100%	100%	None
Seewald <i>et al</i> <sup>[138]</sup>	CR	1	100%	100%	None
Kahaleh <i>et al</i> <sup>[139]</sup>	CR	2	100%	100%	None
Lee <i>et al</i> <sup>[140]</sup>	CR	1	100%	100%	None
Jah <i>et al</i> <sup>[141]</sup>	CR	1	100%	100%	None
Shami <i>et al</i> <sup>[142]</sup>	RS	5	100%	100%	None
Ang <i>et al</i> <sup>[143]</sup>	CR	1	100%	100%	None
Piraka <i>et al</i> <sup>[144]</sup>	PS	7	100%	100%	28%
Noh <i>et al</i> <sup>[145]</sup>	PS	3	100%	100%	None
Puri <i>et al</i> <sup>[146]</sup>	RS	14	100%	93%	None
Itoi <i>et al</i> <sup>[147]</sup>	CR	1	100%	100%	None
Decker <i>et al</i> <sup>[148]</sup>	CR	1	100%	100%	None
Gupta <i>et al</i> <sup>[149]</sup>	RS	20	90%	90%	35%
Ulla-Rocha <i>et al</i> <sup>[150]</sup>	RS	6	100%	100%	None
Varadarajulu <i>et al</i> <sup>[151]</sup>	CR	1	100%	100%	None
Knuth <i>et al</i> <sup>[152]</sup>	CR	1	100%	100%	None
Ramesh <i>et al</i> <sup>[153]</sup>	RS	38	100%	87%	None
Luigiano <i>et al</i> <sup>[154]</sup>	CR	2	100%	100%	None
Total	20 studies	120	100% (90%-100%)	100% (75%-100%)	0% (0%-35%)

<sup>1</sup>Complications include: early and late, procedural and stent related. PS: Prospective study; RS: Retrospective study; CR: Case report.

tinal tract (*i.e.*, subphrenic space, perihepatic, left lobe of the liver, proximal small bowel, left colon, perirectal space, *etc.*). EUS-GD of abdominal (non-peripancreatic) and pelvic collections has been performed in 120 published cases so far, with mean technical and clinical success rates of 99% and 92%, respectively<sup>[135-154]</sup> (LE II b). Overall complication rate was 13% (Table 7). Pelvic collections may present a clinical challenge because of their location, usually surrounded by major organs and anatomic structures (urinary bladder, rectum, prostate, vagina or uterus). All published data available reported the use of a drainage catheter or plastic stents<sup>[136,146,153]</sup> (LE III). Fully covered metal stents have recently been adopted for the drainage of pelvic abscesses<sup>[154]</sup> in order to

minimize the risk of peritoneal leaks, to provide a larger diameter fistula and to avoid early stent occlusion; all these characteristics were shown to increase the clinical success rate and the time to collection resolution (LE III). EUS-guided drainage represents a preferential treatment of deep-seated abdominal fluid collections (LE II b).

## EUS-GUIDED CELIAC PLEXUS

### NEUROLYSIS AND BLOCK

CPN and CPB provide pain relief and reduces narcotic use in patients with intra-abdominal malignancies and chronic pancreatitis<sup>[155]</sup>. The injection of a neurolytic drug into the celiac plexus disrupts the signal transmission to



**Table 8 Endoscopic ultrasound-guided plexus neurolysis/cealic plexus block *n* (%)**

Ref.	Design	Indications	Techniques	Technical success	Clinical success (pain relief)	Complications
Wiersema <i>et al</i> <sup>[167]</sup>	RS	PC ( <i>n</i> = 25) Metastases ( <i>n</i> = 5)	CPN	100%	79%-88%	4 transient diarrhea
Gress <i>et al</i> <sup>[163]</sup>	RCT	CP ( <i>n</i> = 10) CP ( <i>n</i> = 8)	EUS-guided CT-guided	100%	50% 25%	None
Gunaratnam <i>et al</i> <sup>[168]</sup>	PS	PC ( <i>n</i> = 58)	CPN	100%	78%	5 transient abdominal pain
Gress <i>et al</i> <sup>[169]</sup>	PS	CP ( <i>n</i> = 90)	CPB	100%	55%	3 diarrhea
Tran <i>et al</i> <sup>[170]</sup>	RS	PC ( <i>n</i> = 10)	CPN	100%	70%	NR
Ramirez-Luna <i>et al</i> <sup>[171]</sup>	RS	PC ( <i>n</i> = 11)	CPN	100%	72.20%	None
Levy <i>et al</i> <sup>[172]</sup>	RS	PC ( <i>n</i> = 18)	CGN ( <i>n</i> = 17) CGB ( <i>n</i> = 1) CP ( <i>n</i> = 18)	NR NR NR	16/17 (94) 0/1 (0) 4/5 (80)	12 hypotension 6 diarrhea
O'Toole <i>et al</i> <sup>[173]</sup>	RS	PC ( <i>n</i> = 2) CP ( <i>n</i> = 187) PC ( <i>n</i> = 21) CP ( <i>n</i> = 10)	CPB ( <i>n</i> = 189) CPN ( <i>n</i> = 31)	NR NR	NR NR	2 post-procedural pain 1 retroperitoneal abscess 1 hypotension
Santosh <i>et al</i> <sup>[164]</sup>	RCT	CP ( <i>n</i> = 27) CP ( <i>n</i> = 29)	EUS-CPB Percutaneous-CPB	100% -	70% 30%	2 diarrhea
Leblanc <i>et al</i> <sup>[165]</sup>	RCT	CP ( <i>n</i> = 23) CP ( <i>n</i> = 27)	CPB (central) CPB (bilateral)	100%	15/23 (65) 16/27 (59)	None
Sahai <i>et al</i> <sup>[174]</sup>	RS	PC ( <i>n</i> = 34)/ CP ( <i>n</i> = 37) PC ( <i>n</i> = 45)/ CP ( <i>n</i> = 44)	Central CPN Bilateral CPN	100%	45.90% 70.40%	1 adrenal artery bleeding
Sakamoto <i>et al</i> <sup>[175]</sup>	PS	PC ( <i>n</i> = 67)	34CPN 33 BPN	100% 96.90%	72%-79% 19%-78%	None
Wyse <i>et al</i> <sup>[158]</sup>	RCT	PC ( <i>n</i> = 96)	48 CPN 48 control	100% -	60.70% -	None
LeBlanc <i>et al</i> <sup>[160]</sup>	RCT	PC ( <i>n</i> = 29) PC ( <i>n</i> = 21)	CPB (central) CPB (bilateral)	100%	20/29 (69) 17/21 (81)	None
Télliez-Ávila <i>et al</i> <sup>[161]</sup>	RS	PC ( <i>n</i> = 53)	Central ( <i>n</i> = 21) Bilateral ( <i>n</i> = 32)	NR	10/21 (48) 18/32 (56)	None
Iwata <i>et al</i> <sup>[176]</sup>	RS	PC ( <i>n</i> = 47)	CPN	100%	68.10%	NR
Ascunce <i>et al</i> <sup>[177]</sup>	RS	PC ( <i>n</i> = 64)	CPN	100%	50%	1 hypotension
Stevens <i>et al</i> <sup>[166]</sup>	RCT	CP ( <i>n</i> = 40)	Triamcinolone + bupivacaine ( <i>n</i> = 21) Bupivacaine ( <i>n</i> = 19) CPN	100%	68.4%-85.7%	1 severe hypertension 4 pain exacerbation 1 gastric hematoma 3 diarrhea 1 hypotonia 2 post-procedural pain
Wiechowska-Kozłowska <i>et al</i> <sup>[178]</sup>	RS	PC ( <i>n</i> = 29)	CPN	100%	86%	None
Wang <i>et al</i> <sup>[179]</sup>	PS	PC ( <i>n</i> = 23)	Celiac ganglion irradiation	100%	82.60%	None
Leblanc <i>et al</i> <sup>[180]</sup>	PS	PC ( <i>n</i> = 20)	10 mL ( <i>n</i> = 10) 20 mL ( <i>n</i> = 10)	100%	80% 100%	3 nausea and vomiting 2 diarrhea 1 lightheadness
Seicean <i>et al</i> <sup>[181]</sup>	PS	PC ( <i>n</i> = 32)	CPN	100%	75%	NR
Doi <i>et al</i> <sup>[162]</sup>	RCT	PC ( <i>n</i> = 68)	CPN ( <i>n</i> = 34) CGN ( <i>n</i> = 34)	100% 88.20%	45.50% 73.50%	1 GI bleeding 3 hypotension 5 diarrhea 17 pain exacerbation
Total	23 studies	1327	-	100% (88.2%-100%)	71.9% (45.5%-90%)	-

RCT: Randomized controlled trial; PS: Prospective study; RS: Retrospective study; PC: Pancreatic cancer; CP: Chronic pancreatitis; CPN: Celiac plexus neurolysis; CPB: Celiac plexus block; CT: Computed tomography; CGB: Celiac ganglia block; CGN: Celiac ganglia neurolysis; NR: Not reported.

spinal cord and central nervous system. Due to the anatomical location of the celiac plexus around the origin of the celiac trunk and the superior-mesenteric artery, EUS-CPN provides direct, real-time visualization leading to a safer approach than trans-abdominal or posterior access (Table 8).

**EUS-CPN in patients with pancreatic cancer**

**EUS-CPN vs analgesics:** EUS-CPN (8 studies, 283 patients) was demonstrated safe and effective in alleviating refractory pain due to pancreatic cancer: pooled proportion 80.1% (74.5%-85.2%)<sup>[156]</sup> (LE I a). Alcohol-based EUS-CPN was found safe and effective in this

setting: the pooled proportion of patients (5 studies, 119 patients) that experienced pain relief was 72.5%<sup>[157]</sup> (LE I a). In a recent RCT, 96 patients with advanced pancreatic cancer were randomly assigned to early EUS-guided CPN or to conventional pain management; the authors observed greater pain relief in the early EUS-CPN group at three months than in conventional management group [-67% (-87 to -25),  $P = 0.01$ ]<sup>[158]</sup> (LE I b). Finally, compared to opioids, EUS-CPN (6 studies, 358 patients) was demonstrated to reduce pain at four and eight wk [visual analog score -0.42 (-0.70 to -0.13) and -0.44 (-0.89 to -0.01)] and significantly reduced opioid consumptions in the EUS-CPN group ( $P < 0.00001$ )<sup>[159]</sup>. EUS-CPN is superior to analgesic therapy in reducing pain (LE I a).

**Single central injection vs bilateral injections:** LeBlanc *et al.*<sup>[160]</sup> randomized 50 patients with pancreatic cancer to receive one or two injections of alcohol for CPN without observing any difference in onset or duration of pain relief in the two groups<sup>[161]</sup>. There is no difference between central vs bilateral injections in EUS-CPN (LE I b).

**EUS-CPN vs EUS-direct celiac ganglia neurolysis:** Thirty-four patients were assigned to undergoing either EUS-ceeliac ganglia neurolysis (CGN) or classical EUS-CPN. The authors observed higher treatment response rate (73.5% vs 45.5%,  $P = 0.026$ ) and complete response rate (50.0% vs 18.2%,  $P = 0.010$ ) in the EUS-CGN group compared to the EUS-CPN group<sup>[162]</sup>. EUS-CGN is superior to conventional EUS-CPN in inducing pain relief (LE I b).

#### **EUS-CPN and EUS-CPB in patients with chronic pancreatitis**

**EUS-CPN vs analgesics:** In patients with pain due to chronic pancreatitis (9 studies, 376 patients) alcohol-based EUS-CPN provided pain relief in 59.4% (95%CI: 54.5-64.3)<sup>[157]</sup>. EUS-CPN is effective in pain control due to chronic pancreatitis; however, in this setting, due to the relative lower efficacy than in oncologic disease, the development of techniques or new injected drugs seem to be needed (LE I a).

**EUS-CPB vs analgesic:** Meta-analysis for efficacy of steroid-based EUS-guided celiac plexus block (EUS-CPB) in patients with refractory pain due to chronic pancreatitis (6 studies, 221 patients) showed an effective alleviation of abdominal pain only in 51.46% of them<sup>[158]</sup>. EUS-CPB is moderately effective in pain control due to chronic pancreatitis. In this setting, the development of new techniques and/or injected drugs is needed (LE I a).

**EUS-guided vs percutaneous-CPB:** An RCT comparing the safety and efficacy of EUS-guided vs CT-guided celiac plexus block in patients with chronic pancreatitis showed that EUS-CPB was significantly more effective in short-term (50% vs 25% at 4 wk) and long-term (30%

vs 12% at the end of follow-up) pain control<sup>[163]</sup> (LE I b). Another RCT comparing EUS-guided (29 patients) vs percutaneous fluoroscopy-guided (27 patients) CPB with bupivacaine (10 mL) and triamcinolone (3 mL) in patients with chronic pancreatitis demonstrated an improvement in pain scores (visual analog score) in 70% of cases in the EUS group vs 30% of cases in the percutaneous group ( $P = 0.044$ )<sup>[164]</sup> (LE I b). EUS-CPB provides better pain control than percutaneous-CPB (LE I b).

**Single central injection vs bilateral injections:** LeBlanc *et al.*<sup>[165]</sup> randomized 50 patients with chronic pancreatitis to receive one or two injections of bupivacaine and triamcinolone without observing any difference in duration of pain relief or onset of pain in the two groups. There is no difference between central vs bilateral injections in EUS-CPB (LE I b).

**Bupivacaine and triamcinolone vs bupivacaine alone:** In order to evaluate the effect of the addition of triamcinolone to bupivacaine in EUS-CPB, 40 patients were randomized to receive either bupivacaine alone or bupivacaine and triamcinolone. There was no significant difference in pain control between the two groups (14.3% vs 15.8% for controls), therefore the trial was stopped for futility<sup>[166]</sup>. There is no advantage of adding triamcinolone to bupivacaine for EUS-CPB (LE I b).

#### **Complications of EUS-CPN and EUS-CPB**

Most frequent (up to 30% of patients) adverse events related to EUS-CPN/CPB are represented by diarrhea, abdominal pain and hypotension; however, they are usually mild (grade I - II) and self-limiting<sup>[167-181]</sup> (Table 8). Nevertheless, we found reports of serious adverse events related to EUS-CPN/CPB including bleeding, abscess, abdominal ischemia, permanent paralysis and also death (LE III) (Table 9). In our opinion, the risk of serious morbidity and mortality should be weighed against expected benefits particularly in patients with a long life expectancy (*i.e.*, patients with chronic pancreatitis).

## **EUS-GUIDED ETHANOL INJECTION**

### **Pancreatic cystic lesions**

The initial steps for performing EUS-guided ethanol cyst ablation are similar to those for pancreatic EUS-FNA including antibiotic prophylaxis and puncturing the cysts with a 22-gauge needle. After partial or total evacuation of cystic fluid for diagnostic purposes, a volume of ethanol equal to that aspirated should be injected and maintained for 3-5 min. After aspiration of the total amount of ethanol injected, a chemotherapeutic agent (*i.e.*, paclitaxel) may be injected and left inside the cystic cavity<sup>[182-190]</sup> (Table 10).

**Ethanol vs saline:** Ethanol injection with EUS led to a greater reduction in cyst size compared to simple saline injection (43% vs 11%); moreover, ethanol injection re-

**Table 9 Serious adverse events of endoscopic ultrasound-guided celiac plexus neurolysis/ceeliac plexus block**

Ref.	Journal	Year	Complication	Indication	Technique
Gress <i>et al</i> <sup>[247]</sup>	<i>Gastrointest Endosc</i>	1997	1 retroperitoneal bleeding 1 retroperitoneal abscess	CP CP	EUS-CPN EUS-CPB
Mahajan <i>et al</i> <sup>[248]</sup>	<i>Gastrointest Endosc</i>	2002	3 empyema	CP	EUS-CPB
Muscatiello <i>et al</i> <sup>[249]</sup>	<i>Endoscopy</i>	2006	1 retroperitoneal abscess	PC	EUS-CPN
Sahai <i>et al</i> <sup>[174]</sup>	<i>Am J Gastroenterol</i>	2009	1 retroperitoneal bleeding	CP	EUS-CPB
O'Toole <i>et al</i> <sup>[173]</sup>	<i>Endoscopy</i>	2009	1 retroperitoneal abscess	CP	EUS-CPB
Ahmed <i>et al</i> <sup>[250]</sup>	<i>Endoscopy</i>	2009	1 ischemia	CP	EUS-CPN
Shin SK <i>et al</i> <sup>[251]</sup>	<i>Korean J Pain</i>	2010	1 ejaculatory failure	CP	EUS-CPB
Lalueza <i>et al</i> <sup>[252]</sup>	<i>Endoscopy</i>	2011	1 brain abscess	CP	EUS-CPN
Gimeno-Garcia <i>et al</i> <sup>[253]</sup>	<i>Endoscopy</i>	2012	1 ischemia/death	CP	EUS-CPN
Fujii <i>et al</i> <sup>[254]</sup>	<i>Endoscopy</i>	2012	1 spinal cord infarction/paralysis	PC	EUS-CPN-G
Mittal <i>et al</i> <sup>[255]</sup>	<i>Neurology</i>	2012	1 spinal cord infarction/paralysis	PC	EUS-CPN-G
Loeve <i>et al</i> <sup>[256]</sup>	<i>Gastrointest Endosc</i>	2013	1 gastric necrosis/death	PC	EUS-CPN
Jang <i>et al</i> <sup>[257]</sup>	<i>Clin Endosc</i>	2013	1 hepatic-bowel infarction/death	PC	EUS-CPN
Doi <i>et al</i> <sup>[162]</sup>	<i>Endoscopy</i>	2013	1 GI bleeding (puncture site)	PC	EUS-CGN

CP: Chronic pancreatitis; PC: Pancreatic cancer; CPN: Celiac plexus neurolysis; CPB: Celiac plexus block.

**Table 10 Endoscopic ultrasound-guided ethanol injection of abdominal solid and cystic tumors**

Ref.	Design	Indications	Lesion size (mm)	Techniques	Clinical success	Complications
Gan <i>et al</i> <sup>[187]</sup>	PS	Pancreatic cystic lesions (n = 25)	6-30	Ethanol	35%	None
Oh <i>et al</i> <sup>[185]</sup>	PS	Pancreatic cystic lesions (n = 14)	17-52	Ethanol and paclitaxel	79%	1 acute pancreatitis 6 hyperamylasemia 1 abdominal pain
Oh <i>et al</i> <sup>[182]</sup>	PS	Septated pancreas cysts (n = 10)	20-68	Ethanol and paclitaxel	60%	1 acute pancreatitis
DeWitt <i>et al</i> <sup>[183]</sup>	RCT	Pancreatic cystic lesions (n = 42)	10-58	Ethanol vs saline	33%	1 acute pancreatitis 5 abdominal pain 1 cystic bleeding
DeWitt <i>et al</i> <sup>[184]</sup>	PS	Pancreatic cystic lesions (n = 12)	10-50	Ethanol	75% at follow-up	-
Oh <i>et al</i> <sup>[186]</sup>	PS	Pancreatic cystic lesions (n = 52)	17-68	Ethanol and paclitaxel	62%	1 acute pancreatitis 1 abdominal pain 1 fever 1 splenic vein thrombosis
DiMaio <i>et al</i> <sup>[189]</sup>	RS	Pancreatic cystic lesions (n = 13)	20.1 ± 7.1	Ethanol (single/multi)	38%	1 abdominal pain
Oh <i>et al</i> <sup>[190]</sup>	RS	Pancreatic cystic lesions (n = 1)	5.2	Ethanol 99% 28 mL + paclitaxel	Failure, underwent surgery	Portal vein thrombosis
Jurgensen <i>et al</i> <sup>[192]</sup>	RS	Pancreatic NET (n = 1)	13	Ethanol 95% 8 mL	Complete remission	Pain + lipase increase
Muscatiello <i>et al</i> <sup>[193]</sup>	RS	Pancreatic NET (n = 1)	11 and 7	Ethanol 40% 2 mL	No recurrence at 18 mo	Small pancreatic necrosis
Deprez <i>et al</i> <sup>[194]</sup>	RS	Pancreatic NET (n = 1)	13	Ethanol 98% 3.5 mL	Complete remission	Hematoma and duodenal ulcer
Vleggaar <i>et al</i> <sup>[195]</sup>	RS	Pancreatic NET (n = 1)	10	Ethanol 96% 0.3 mL	Asymptomatic at 6 mo	None
Levy <i>et al</i> <sup>[191]</sup>	RS	Pancreatic NET (n = 5)	8-21	Ethanol 95-99% 0.1-3 mL	60% symptoms resolution	None
Barclay <i>et al</i> <sup>[196]</sup>	RS	Solid Hepatic Metastasis (n = 1)	33	Ethanol 98% 6 mL	Good condition at 5.5 yr	Liver hematoma
Gunter <i>et al</i> <sup>[197]</sup>	RS	GI stromal tumor (n = 1)	40	Ethanol 95% 1.5 mL	Complete remission	Abdominal pain Mucosal ulceration
Hu <i>et al</i> <sup>[198]</sup>	RS	Liver metastasis (n = 1)	35	Ethanol 100% 10 mL	Local control and decrease in size	Fever
Artifon <i>et al</i> <sup>[199]</sup>	RS	Left adrenal metastasis (n = 1)	50	Ethanol 98% 15 mL	Palliation of related pain	None
DeWitt <i>et al</i> <sup>[200]</sup>	RS	Metastatic lymph node (n = 1)	10-11	Ethanol 4 + 2 mL	Locally successful	None
Total (cystic lesion)	8 studies	169 patients	6-68	-	60% (33%-79%)	-

RCT: Randomized controlled trial; PS: Prospective study; RS: Retrospective study; NR: Not reported; NET: Neuroendocrine tumor.

sulted in complete cyst ablation in 33% of cases (12 out of 36)<sup>[183]</sup> (LE I b). Follow-up by CT scan at 2 years of patients who had obtained complete cyst ablation after

treatment showed persistent resolution of pancreatic cystic lesions in 75% of cases<sup>[184]</sup> (LE II b). Ethanol injection and lavage induces a significantly greater reduction in cyst

Table 11 Endoscopic ultrasound-guided tumor ablation

Ref.	Design	Indications	Techniques	Type	Tumor response	Complications
Chang <i>et al</i> <sup>[202]</sup>	PS	Pancreatic cancer ( <i>n</i> = 8)	Injection	Cytoimplant	2 partial; 1 minor	None
Hecht <i>et al</i> <sup>[203]</sup>	PS	Pancreatic cancer ( <i>n</i> = 21)	Injection	ONYX-015 + <i>iv</i> gemcitabine	2 partial; 2 minor; 6 stable; 11 progression	2 sepsis 2 duodenal perforations
Chang <i>et al</i> <sup>[211]</sup>	RS	Pancreatic cancer ( <i>n</i> = 1)	Injection	TNFERade + chemoradiotx	Surgical resection	None
Hecht <i>et al</i> <sup>[205]</sup>	PS	Pancreatic cancer ( <i>n</i> = 50)	Injection (27 EUS-guided)	TNFERade + chemoradiotx	1 complete; 3 partial; 4 minor; 12 stable	6 GI bleeding 6 deep vein thrombosis 2 pulmonary embolism 2 pancreatitis 6 cholangitis
Irisawa <i>et al</i> <sup>[204]</sup>	PS	Pancreatic cancer ( <i>n</i> = 7)	Injection	Immature dendritic cells	2 mixed; 2 stable; 3 progressive	None
Hanna <i>et al</i> <sup>[207]</sup>	PS	Pancreatic cancer ( <i>n</i> = 9)	Injection (6 EUS-guided)	BC-819 + chemoradiotx	2 surgically resectable; 3 partial	None
Chang <i>et al</i> <sup>[206]</sup>	PS	Esophageal cancer ( <i>n</i> = 24)	Injection	TNFERade	6 complete; 2 stable	5 thromboembolic events (highest dose)
Arcidiacono <sup>[208]</sup>	PS	Pancreatic cancer ( <i>n</i> = 22)	Cryothermal Ablation	EUS-CTP	6 partial response (only 6 patients analyzed)	3 hyperamylasemia
Maier <i>et al</i> <sup>[212]</sup>	PS	Head/neck cancer ( <i>n</i> = 21)	Brachytx	Ir-192 needles	4 full; 15 partial; 3 none	None
Lah <i>et al</i> <sup>[213]</sup>	RS	Metastatic celiac lymph nodes ( <i>n</i> = 1)	Brachytx	I-125 seeds	Response	None
Martinez-Monge <i>et al</i> <sup>[214]</sup>	RS	Metastatic mediastinal lymph node ( <i>n</i> = 1)	Brachytx	I-125 seeds	Response	None
Sun <i>et al</i> <sup>[209]</sup>	PS	Pancreatic cancer ( <i>n</i> = 15)	Brachytx	I-125 seeds	4 partial; 3 minor; 5 stable; 3 progressive	1 site infection 3 hematologic side effects
Jin <i>et al</i> <sup>[210]</sup>	PS	Pancreatic cancer ( <i>n</i> = 22)	Brachytx	I-125 seeds	4 partial; 10 stable	1 seed migration

RCT: Randomized controlled trial; PS: Prospective study; RS: Retrospective study; NR: Not reported; CTP: Cryothermal probe; GI: Gastrointestinal.

size and allows a significantly higher rate of cyst ablation than saline alone (LE I b).

**Ethanol plus paclitaxel:** In their experience on 52 patients with uniloculated or oligoloculated pancreatic cyst treated with ethanol lavage followed by paclitaxel injection, Oh *et al*<sup>[186]</sup> observed complete resolution in 62% of patients after 1-year follow-up. The authors identified small cyst size as a positive predictive factor of treatment response. Addition of paclitaxel to ethanol injection is safe and effective and leads to a greater treatment rate of pancreatic cystic lesions compared to ethanol alone (LE II b).

### Solid lesions

EUS-guided injection of ethanol has been applied to a variety of solid tumors including pancreatic endocrine tumors, hepatic metastases, and submucosal tumors<sup>[191-200]</sup>. In a single-center RS, Levy *et al*<sup>[191]</sup> reported safety and efficacy of EUS-guided ethanol injection in five patients with pancreatic insulinoma. The authors obtained symptoms resolution in 60% of patients with no complications<sup>[191]</sup> (LE III). Ethanol injection is feasible and safe in solid pancreatic insulinomas (LE III).

## EUS-GUIDED TUMOR ABLATION

### EUS-guided fine needle injection

EUS-fine needle injection (FNI) is a simple technique to deliver chemotherapeutic agents into tumoral tissue for the treatment of locally advanced pancreatic or esophageal cancer. The technical outcome of all the studies about EUS-FNI reached 100%, paralleling the ability of performing EUS-FNA for cytological diagnosis. However, the clinical outcome varied greatly according to the different chemical or biological agents being tested<sup>[201]</sup> (Table 11).

**Allogeneic mixed lymphocyte culture:** The first study assessing EUS-FNI for pancreatic cancer tested the safety and efficacy of allogeneic mixed lymphocyte culture in locally advanced pancreatic adenocarcinoma in 8 patients. The procedure (single session of EUS-guided injection) was safe and two partial responses and one minor response were reported (median survival 13.2 mo)<sup>[202]</sup> (LE II b).

**Adenovirus ONYX-015:** ONYX-015, a modified adenovirus (deletion in the E1B gene) which replicate in tumor

cells leading to cell death, was used for EUS-FNI in pancreatic cancer in combination with systemic gemcitabine. The authors enrolled 21 patients in this phase I study and reported two patients with partial regression and two with minor response. However, 4 serious adverse events were observed (two sepsis and two duodenal perforations)<sup>[203]</sup> (LE II b).

**Immature dendritic cells:** Irisawa *et al.*<sup>[204]</sup> reported a pilot study (phase I) with injection of immature dendritic cells (DCs). DCs were used for EUS-FNI in view of their potent induction of primary T-cell response against tumor antigens. Among 7 patients with locally advanced pancreatic adenocarcinoma, one complete and three partial responses were reported. No adverse events were described<sup>[204]</sup> (LE II b).

**TNFERade:** EUS-FNI of TNFERade, a replication-deficient adenovirus vector carrying the tumor necrosis factor- $\alpha$  gene, was tested in a multicenter study on 50 patients with locally advanced pancreatic cancer in combination with systemic fluorouracil. The authors observed 1 complete response, 3 partial responses, and 12 patients with stable disease after treatment. Interestingly, seven patients became suitable for surgery after EUS-FNI and 6 of them underwent R0 resection. According to the authors, an RCT is warranted to further assess these encouraging results<sup>[205]</sup> (LE II b).

The efficacy of EUS-FNI of TNFERade was also assessed in 24 patients with locally advanced but still resectable esophageal cancer (20% stage II, 80% stage III). EUS-FNI of TNFERade was combined with cisplatin, 5-fluorouracil and radiation therapy. Six complete responses and 2 stable diseases were observed. The median survival was 47.8 mo and 5-year survival and disease-free survival rates were 41% and 38%, respectively. Additionally, EUS-FNI proved to be safe<sup>[206]</sup> (LE II b).

**BC-819:** The safety, tolerability and preliminary efficacy of EUS-FNI of BC-819, a DNA plasmid developed to target the expression of diphtheria-toxin gene under the control of H19 regulatory sequences, was recently tested in 6 patients with pancreatic cancer in combination with chemoradiotherapy. Three patients showed partial response and other two patients who were downstaged were able to undergo surgical resection<sup>[207]</sup>. Intratumoral EUS-FNI in patients with advanced pancreatic and esophageal cancer is technically easy, safe and can induce tumor downstaging in some cases (LE II b).

### **EUS-guided cryothermal ablation**

The safety and efficacy of cryothermal ablation was assessed using a newly developed cryotherm probe (CTP) in 22 patients with locally advanced pancreatic cancer. CTP is a large bore flexible bipolar device that combines radiofrequency with cryogenic cooling in the same session. EUS-guided CTP ablation was feasible in 16 patients. CT scan was performed in all cases after treatment;

in 6/16 patients a reduction in tumor size was clearly seen. The procedure was well tolerated in all cases<sup>[208]</sup> (LE II b).

### **EUS-guided brachytherapy**

The feasibility, safety and efficacy of EUS-guided implantation of radioactive seeds in patients with locally advanced pancreatic cancer were assessed in a few studies<sup>[209-214]</sup>. Partial tumor response ranged from 13.6% to 27% while a stable disease was observed in 45.5%-53% of cases in two pilot studies<sup>[209,210]</sup>. In both series, up to 30% of patients reported transient pain reduction within the first period after treatment. Adverse event rate range was 0%-20% (pancreatitis and pseudocyst formation) in association to systemic, non-EUS-related, adverse events (LE II b). EUS-guided CTP ablation and brachytherapy are feasible in a subset of patients with locally advanced pancreatic cancer. However, their safety and clinical outcome have to be further investigated (LE II b).

### **EUS-guided fiducial placement**

Imaging-guided radiation therapy is based upon a real-time tracking system to target the tumor to be irradiated. In order to minimize irradiation of adjacent normal tissue in pancreatic malignancies, the placement of radiopaque fiducials inside or near the tumor allows a radiographic marking enabling precise tumor targeting. Firstly, fiducials were placed in patients with advanced pancreatic cancer were placed with surgical or radiological techniques. In the last decade, the less invasive EUS-guided fiducial placement was shown to be safe and precise<sup>[215-227]</sup> (Table 12).

**Safety and effectiveness:** Two PSs enrolling a total of 101 patients with locally advanced or recurrent pancreatic cancer reported high technical and clinical success rates (88%-90%). Overall complication rate was low with only few minor adverse events (one patient experienced minor bleeding from the site of EUS needle entrance and one experienced mild pancreatitis). Migration of the gold fiducials was reported in 7% of cases<sup>[216,217]</sup> (LE II b).

**Traditional vs coiled fiducials:** Khashab *et al.*<sup>[218]</sup> compared the technical success, safety, visibility and migration of two different types of fiducials (traditional *vs* coiled). In their RS, no differences were observed in visibility, degree of fiducial migration, number of fiducial placement, technical difficulty or complication rate (LE III).

**Ideal fiducial geometry:** A recent study compared the achievement of the ideal fiducial geometry (IGF) (defined as the placement of 3 fiducials with at least 2 cm of distance, at least 15 degrees angle, and non-planar placement) in 39 patients who underwent EUS-guided fiducial placement *vs* 38 who underwent surgical fiducial placement. In this RS, the authors identified a significantly higher rate of IGF reached with surgical *vs* EUS placement (47% *vs* 18%,  $P = 0.0011$ ). However, it was ob-

**Table 12 Endoscopic ultrasound-guided fiducial placement *n* (%)**

Ref.	Design	Indications	Techniques	Technical success	Needle	Complications
Pishvaian <i>et al</i> <sup>[215]</sup>	PS	Abdominal/mediastinal cancer ( <i>n</i> = 13)	Fiducial placement	11/13 (84.6)	19 Gauge	1 infection
Varadarajulu <i>et al</i> <sup>[222]</sup>	RS	Pancreatic cancer ( <i>n</i> = 9)	Fiducial placement	9/9 (100)	NR	None
DiMaio <i>et al</i> <sup>[223]</sup>	RS	Abdominal/mediastinal cancer ( <i>n</i> = 30)	Fiducial placement	29/30 (97)	22 Gauge	None
Sanders <i>et al</i> <sup>[217]</sup>	PS	Pancreatic cancer ( <i>n</i> = 51)	Fiducial placement	46/51 (90)	19 Gauge	1 mild pancreatitis
Park <i>et al</i> <sup>[216]</sup>	PS	Pancreatic cancer ( <i>n</i> = 57)	Fiducial placement	50/57 (88)	19 Gauge	None
Ammar <i>et al</i> <sup>[224]</sup>	RS	Abdominal cancer/lymph nodes ( <i>n</i> = 13)	Single fiducial marker	9/9 trans-gastric 4/4 trans-duodenal	22 Gauge	None
Varadarajulu <i>et al</i> <sup>[225]</sup>	PS	Pancreatic cancer ( <i>n</i> = 2)	Fiducial placement	2/2 (100)	19 Gauge flexible	None
Khashab <i>et al</i> <sup>[218]</sup>	RS	Pancreatic cancer ( <i>n</i> = 39)	Fiducial placement (traditional <i>vs</i> coiled)	39/39 (100)	19 and 22 Gauge	None
Law <i>et al</i> <sup>[226]</sup>	RS	Small pancreatic NET ( <i>n</i> = 2)	Fiducial placement	2/2 (100)	22 Gauge	None
Majumder <i>et al</i> <sup>[219]</sup>	RS	Pancreatic cancer ( <i>n</i> = 39)	Fiducial placement	35/39 (89.7)	19 Gauge	1 mild pancreatitis 4 abdominal pain
Yang <i>et al</i> <sup>[220]</sup>	RS	Prostate cancer ( <i>n</i> = 16)	Fiducial placement	16/16 (100)	19 Gauge	None
Yang <i>et al</i> <sup>[221]</sup>	RS	Prostate cancer recurrence ( <i>n</i> = 6)	Fiducial placement	6/6 (100)	19 Gauge	None
Trevino <i>et al</i> <sup>[227]</sup>	RS	Rectal cancer ( <i>n</i> = 1)	Fiducial placement	3/3 (100)	19 Gauge (forward-view EUS)	None
Total	13 studies	278	-	100% (84.6%-100%)	-	0%

RCT: Randomized controlled trial; PS: Prospective study; RS: Retrospective study; NR: Not reported; NET: Neuroendocrine tumor.

served that despite the lower IGF rate in the EUS group, fiducial tracking for irradiation therapy was successful in a similar percentage of patients from the two groups (> 80%)<sup>[219]</sup> (LE III). EUS-guided fiducial placement is safe and leads to technical and clinical success in about 90% of patients (LE II b).

**Non-pancreatic cancer:** Two recent retrospective case series reported the feasibility and safety of fiducial placement in 16 patients with prostate cancer and in 6 with prostate cancer recurrence. The authors reported extremely high success rates (16/16 and 6/6 respectively) with no incidence of adverse events<sup>[220,221]</sup> (LE III). EUS-guided fiducial placement was feasible and safe in patients with prostate cancer or prostate cancer recurrence (LE III).

## EUS-GUIDED VASCULAR INTERVENTIONS

EUS combined with color/power Doppler allows precise identification of vascular anatomy, potential high risk vessels with/without portal hypertension, and occult sources of bleeding such as Dieulafoy's lesions and pseudoaneurysms. Moreover, EUS provides direct access to vascular structures next to gastrointestinal wall, allowing precise vascular interventions<sup>[228-246]</sup> (Table 13).

### EUS-guided treatment of non-variceal bleeding

The efficacy of EUS-guided treatments of non-variceal upper gastrointestinal bleeding was reported only in form of small case series and case reports. Fockens *et al*<sup>[229]</sup> first reported about the usefulness of EUS in the diagnosis

of small abnormal vessels in 8 patients with Dieulafoy's lesions. In 50% of cases it was possible to perform EUS-guided injection of sclerosing agent into the aberrant vessels<sup>[229]</sup> (LE III).

### EUS-guided treatment of portal hypertension

**Endoscopic vs EUS-guided sclerotherapy of esophageal collateral veins:** An RCT compared the safety and efficacy of EUS-guided and endoscopic sclerotherapy (ethanolamine oleate injection) in 50 patients affected by liver cirrhosis. The authors did not observe any difference in variceal eradication, number of sessions needed to achieve the eradication, variceal recurrence and adverse event rates<sup>[230]</sup> (LE I b). EUS-guided sclerotherapy does not confer any significant advantage in terms of safety and efficacy compared to classical endoscopic sclerotherapy (LE I b).

**Gastric variceal bleeding:** In a RS, EUS-assisted cyanoacrylate (CYA) injection until obliteration of all gastric varices collateral was compared to an historical group of cirrhotic patients who underwent standard endoscopic injection, only in case of recurrent bleeding. While early re-bleeding rate was similar in the two groups (7.4% *vs* 12.8%, respectively, *P* = NS), late recurrent bleeding was significantly reduced in patients who underwent CYA injection under EUS control to check for complete obliteration (18.5% *vs* 44.7%, *P* = 0.0053, OR = 0.28)<sup>[231]</sup> (LE II b). EUS guidance allows an higher rate of gastric variceal obliteration and reduces recurrent bleeding (LE II b).

**Coil embolization vs CYA injection for gastric varices:** A multicenter RS compared feasibility, safety and applicability of coil embolization *vs* sclerotherapy (CYA

**Table 13 Endoscopic ultrasound-guided vascular interventions *n* (%)**

Ref.	Design	Indications	Techniques	Technical success	Rebleeding	Complications
Fockens <i>et al</i> <sup>[229]</sup>	RS	Dieulafoy's lesion ( <i>n</i> = 4)	Polidocanol injection	4/4 (100)	2/4 (50)	None
Levy <i>et al</i> <sup>[234]</sup>	RS	Dieulafoy's lesion ( <i>n</i> = 1)	Alcohol 99% injection	1/1 (100)	No	None
Gonzalez <i>et al</i> <sup>[235]</sup>	RS	Dieulafoy's lesion ( <i>n</i> = 2)	Polidocanol or CYA injection	2/2 (100)	No	None
Levy <i>et al</i> <sup>[234]</sup>	RS	Various ( <i>n</i> = 4)	Alcohol 99% or CYA injection	4/4 (100)	No	None
Gonzalez <i>et al</i> <sup>[235]</sup>	RS	Pseudo-aneurysm ( <i>n</i> = 3)	CYA injection	3/3 (100)	No	None
Gonzalez <i>et al</i> <sup>[235]</sup>	RS	Gastric varices ( <i>n</i> = 2)	CYA injection	2/2 (100)	No	None
Lee <i>et al</i> <sup>[231]</sup>	RS	Gastric varices ( <i>n</i> = 101)	EUS-assisted CYA injection	-	Early 4/54 (7.4) Late 10/54 (18)	None
Lahoti <i>et al</i> <sup>[236]</sup>	RS	Esophageal varices ( <i>n</i> = 5)	Sclerotherapy	5/5 (100)	No	1 esophageal stricture
Romero-Castro <i>et al</i> <sup>[237]</sup>	RS	Gastric varices ( <i>n</i> = 5)	CYA injection	5/5 (100)	No	None
De Paulo <i>et al</i> <sup>[230]</sup>	RCT	Esophageal varices ( <i>n</i> = 50)	Endo <i>vs</i> EUS-guided CYA injection	24/25 (96)	2/24 recurrence of varices (8.3)	None
Levy <i>et al</i> <sup>[238]</sup>	RS	Choledochojejunal anastomotic varices ( <i>n</i> = 1)	Coil embolization	1/1 (100)	No	None
Romero-Castro <i>et al</i> <sup>[239]</sup>	RS	Gastric varices ( <i>n</i> = 4)	Coil embolization	3/4 (75)	No	None
Binmoeller <i>et al</i> <sup>[233]</sup>	RS	Gastric varices ( <i>n</i> = 30)	CYA injection + coil embolization	30/30 (100)	4/24 (16.6)	None
Romero-Castro <i>et al</i> <sup>[232]</sup>	RS	Gastric varices ( <i>n</i> = 30)	CYA injection ( <i>n</i> = 19) <i>vs</i> coils ( <i>n</i> = 11)	97.4 % <i>vs</i> 90.9%	NR	9 CYA embolization; 1 chest pain; 1 fever; 1 variceal bleeding
Weilert <i>et al</i> <sup>[240]</sup>	RS	Rectal varices ( <i>n</i> = 1)	CYA injection plus coils	100%	No	None
Gonzalez <i>et al</i> <sup>[241]</sup>	RS	Splenic artery aneurysm ( <i>n</i> = 1)	CYA injection	1/1 (100)	No	None
Roberts <i>et al</i> <sup>[242]</sup>	RS	Visceral pseudoaneurysm ( <i>n</i> = 1)	HistoAcryl injection	1/1 (100)	No	None
Roach <i>et al</i> <sup>[243]</sup>	RS	SMA aneurysm ( <i>n</i> = 1)	Thrombin injection	1/1 (100)	No	None
Chaves <i>et al</i> <sup>[244]</sup>	RS	SMA aneurysm ( <i>n</i> = 1)	Thrombin injection	1/1 (100)	No	None
Robinson <i>et al</i> <sup>[245]</sup>	RS	Splenic artery aneurysm ( <i>n</i> = 1)	Thrombin injection	1/1 (100)	No	None
Lameris <i>et al</i> <sup>[246]</sup>	RS	Visceral pseudoaneurysm ( <i>n</i> = 1)	Thrombin + collagen injection	1/1 (100)	No	None

RCT: Randomized controlled trial; PS: Prospective study; RS: Retrospective study; NR: Not reported; CYA: Cyanoacrylate; SMA: Superior mesenteric artery.

injection) under EUS guidance. Thirty patients (11 coil group *vs* 19 CYA group) underwent EUS-guided treatment for gastric varices. The rate of variceal obliteration was similar in the two groups (90.9% *vs* 94.7%, respectively) without differences in number of EUS sessions. Eleven patients (11/19) in the sclerotherapy group experienced adverse events; in 9 of them an asymptomatic pulmonary glue embolism was found on CT scan, while 1 patient experienced fever and another experienced chest pain; on the other hand, only one patient treated with coil embolization experienced an adverse event (esophageal variceal bleeding). The comparison among the two treatment groups demonstrated a significantly lower incidence of any grade adverse events in the embolization group (58% *vs* 9%, *P* < 0.01); only 3 patients, two in the CYA and one in the coil group, experienced symptomatic adverse events<sup>[232]</sup> (LE II b).

**Combined coil embolization and CYA injection for gastric varices:** The authors reported about 30 patients who underwent EUS-guided trans-esophageal combined embolization and sclerotherapy of gastric varices using in the majority of cases a forward-view echoendoscope.

Successful treatment was achieved in all cases (30 out of 30, 100%) after a mean of 1.3 EUS sessions, including 2 cases with active bleeding. Rebleeding occurred in 16% of cases and no procedure-related adverse events were reported<sup>[233]</sup> (LE III). EUS-guided coil embolization and CYA injection are both effective for gastric varices treatment in patients with cirrhosis (LE II b). While both sclerotherapy and embolization monotherapy present a high complication rate, combined coil embolization and CYA injection seems to be safe and effective in patients with gastric varices (LE III).

## CONCLUSION

Several EUS-guided treatments are now available in endosonographer's armamentarium. The usefulness of EUS-GD of PFCs and of EUS-CPN has been well established in studies with high LE. Other techniques including EUS-guided biliary drainage have been tested only in studies with medium-low LE and thus should still be performed either in referral centers by experienced endosonographers or in investigational/research settings. Well-designed RCTs are warranted to further elucidate

the safety and benefits of EUS-guided treatments in comparison to the standards of care.

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